Research Article

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Designing Polymer-based Mucosa Membranes: Biomimicking

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Abstract

Mucoadhesion develops when a polymer adheres to the mucosal membrane through chemical or physical interactions. Adhesive materials are often employed in the manufacture of dosage forms for transmucosal drug administration via oral, nasal, esophageal, buccal and vaginal routes. This review covers some of the most prevalent synthetic methods for improving the mucoadhesive characteristics of polymeric materials. The buccal film and the oral dose form are two of these administration methods. Medication with a high blood perfusion rate can easily pass through the mucosal barrier of the mouth (oral mucosa). Drugs with low bioavailability and short half-life are simpler to administer. Buccal films, as opposed to traditional drug delivery systems, enable for the regulated and prolonged release of topical pharmaceuticals and are favoured over alternative approaches for delivering medications that are at risk of being lost because to the first pass effect, reduced permeability, enzyme degradation along with the gastrointestinal system's changing environment. Superior mucoadhesive qualities are found in hydrophilic polymers that have charged groups and/or non-ionic functional groups that can establish hydrogen bonds with mucosal surfaces. There are multiple ways for assessing the mucoadhesive characteristics of different dosage formulations. This review provides an overview of the properties of mucoadhesive and mucus gel, as well as the most commonly used procedures.

Keywords: glycopolymer, mucosa, membranes, collagen, cellulose, hydrogel, buccal

1. Introduction

When drugs are delivered orally, oromucosally, nasally, ocularly, rectally, or vaginally, they must pass through the body's 'mucosal membrane' to enter systemic circulation. The digestive tract, the respiratory tract, the eyes, and the reproductive system all have moist linings, known as mucosal membranes. Secretory mucus is 95% water, 5% mucins, and 1% inorganic ions, with various minor constituents making up the remaining percent. While both secretory and membrane-bound mucins have hydrophobic domains that are binding them to the epithelial surface, they are distinctly different from

one another because the former possess hydrophobic domains while the latter lack them. The glycoproteins of mucins have oligosaccharide side chains, and the majority of the molecules have an about 80% carbohydrate content. Generally, medications that are absorbed through the mucosal membranes have low bioavailability, limiting pharmaceutical effectiveness. One way to boost drug absorption is to utilise polymeric polymers known as mucoadhesive

polymers, which bind to the mucosal surface and retain a dose form. Because mucoadhesive dosage forms generally remain in place on ex vivo animal tissues, they are usually assessed by their adherence to or retention on the tissue. Furthermore, obtaining animal tissues is challenging, as the tissues are different and sometimes demand the sacrifice of an animal. In order to conduct mucoadhesion testing, it is important to build a synthetic mucosa-mimetic to replace ex vivo mucosal tissue. Reduced usage of laboratory animals in mucoadhesion testing and a more uniform substrate that is easier to handle are the benefits of this innovation.1–4

2.a.Oral Mucosa

The oral mucosa is composed of a connective dermis and a stratified squamous epithelium. It lacks hair follicles, sebaceous and sweat glands, however, in comparison to skin tissues 5,6. There are salivary glands that are related via the mouth epithelium and are not located on the skin. 7Thus, the development of an oral mucosal tissue model is focused on controlling and optimizing mechanical properties while preserving oral mucosal cell adhesion, proliferation, and differentiation. 8–11

2.b. Membrane Designs

2.b.1. Glycopolymer hydrogels

These glass-bound glycopolymer hydrogels are derived from hydrogels that are attached to glass using glycosaminoglycans which resemble the oligosaccharide chains of mucin. A ‘bottlebrush' oligosaccharide structure masks the protein backbone. This research shows that glycopolymers, polymers holding pendant carbohydrate groups, may imitate glycoproteins well, including mucin 12. The glycomonomer N-acryloyl-D-glucosamine (AGA) was synthesised so as to replicate the neutral sugars present in the side chains of mucins 13,14

The structure was confirmed by the chemical shifts used in mass spectroscopy, H NMR, FTIR and 13C NMR. In the presence of a cross-linker, glycopolymer hydrogels may be produced by thermally-initiated radical polymerization in which AGA is copolymerized with 2-hydroxyethyl methacrylate (HEMA) 15

2.b.2. Collagen gels

Eight volumes of ice-cold bovine collagen I solution were combined with one volume of 10 Hanks' balanced salt solution to create the equivalent of the lamina propria. After neutralisation with 1 M NaOH, normal human oral fibroblasts (NHOFs) were added. 29

2.b.3. Poly(acrylic acid) based hydrogels

Poly(acrylic acid), triethoxysilane (3-aminopropyl), N-(3-dimethylaminopropyl)-N0-ethylcarbodiimide hydrochloride, methoxyl methylcellulose (Methocel 60 HG) at a concentration of 28–30%, Carbopol 940, deionized water was used. The viscosity of 2% methylcellulose in water is between 35–55 mPa seconds. All polymer solutions are obtained by dissolving the polymer in deionized water. By adding 0.1 mol L1 HCl or NaOH to the polymer solutions, the pH was adjusted. B4Na2O7, H3BO4, and NaOH were combined to create buffers with the desired pH, or citric acid, sodium hydroxide, and HCl were combined to create buffers with the desired pH.36

2.b.4. GelMA Hydrogels

Compounds used were Gelatin (Type A from porcine skin),
2-Hydroxy-1-(4-(hydroxyethoxy)phenyl)-2-methyl-1-propanone and methacrylic anhydride (MA) as a photoinitiator for photocuring. Dulbecco’s phosphate buffered saline (DPBS) and Dialysis tubes were also required.

3. Buccal Membrane

3.a. Overview

Extensive permeation experiments are required for buccal formulation development and assessment. The production of freshly excised mucosa from killed animals is required for in vitro experiments. The mucosa should be employed right away for permeation testing. Permeability variation may also develop as a result of tissue preparation changes. The current in vitro evaluation technique must be improved if consistent results are to be obtained, animals are to be spared, and development processes for buccal items are to be sped up.41

Buccal administration overcomes a number of the oral route's disadvantages, including a faster start of action and increased bioavailability, by avoiding pre-systemic and chemical processing in the gastrointestinal tract. In addition, buccal administration is believed to be easy to accept by patients, since it is readily accessible, convenient, noninvasive, and almost universal among patients. Additionally, buccal mucosa has low buccal permeability and is able to keep the delivery system in place in the buccal cavity. These features make buccal mucosa an excellent delivery route for long-term and regulated drug administration. Low penetration of medicines via the buccal mucosa, specifically the epithelial layer, makes buccal systemic distribution more restricted 42,43. Buccally impermeable non-lipophilic medicines are not often able to be delivered by this route. Because the medicine must pass through the epithelium, absorption throughout the whole body surface is ensured, as the huge highly vascularized region provides access to the whole circulatory system. To obtain a better delivery, increase of transmucosal penetration is recommended. By offering reversible and safe means of decreasing the physical barriers of mucosal tissue, permeation enhancers increase buccal delivery, hence increasing the rate of administration. Tissue diffusion studies of newly excised animal mucosa (porcine, rabbits, hamster cheeks, and dogs) can be used to evaluate buccal delivery effectiveness in vitro. 60–62 Nevertheless, the utilisation of animal mucosa has its own restrictions, including animal sacrifice, the difficulty in procuring fresh excised tissue, and the need for additional care in order to preserve the tissue. Another way to evaluate for permeability is to utilise cultured buccal epithelium 42–44

Research on artificial membranes that mimic natural mucosa is now being developed to serve as an alternative to natural membranes for assessment. More humane techniques will save animals, labour, time, and costs associated with the delivery of buccal implants. In addition, artificial membranes may serve as a fast and simple screening procedure when several formulations have to be reviewed before carrying out the animal testing. To yet, however, these investigations have not helped to correlate artificial membrane diffusion data with actual buccal tissues.45,46

3.b.1. Polymeric and cellulosic membranes

The current study examined the use of model polymeric membranes, cellulose acetate-nitrate and cellulose acetate, as a quick screening alternative to genuine mucosa. For carvedilol, a hydrophobic medication, permeability coefficient and steady-state flow were evaluated in natural and artificial membranes.47 The compounds used were carvedilol, camphor, sodium taurodeoxycholate hydrate, sodium taurocholic hydrate, l-menthol, l-α-phosphatidylethanolamine, and propylene glycol, di-sodium hydrogen orthophosphate anhydrous.48

4. Synthesis Procedure

4.1. Glycopolymer hydrogels

Mucoadhesion is a complicated process that is facilitated in part by hydrogen bonding, hydrophobic and electrostatic interactions between the mucosa and mucoadhesive. Solid dosage forms (like tablets) also cling to mucosal membranes by wetting of the dosage form, interpenetration of polymer chains, partial dehydration of the tissue and chemical interactions 11 .The gel can be covalently bonded to the glass if the polymerization is performed in the presence of silanized glass having thiol groups on its surface.10,16

In order for the polymer chains to spread from the glass's surface, the thiol plays the role of a chain transfer agent. In order to synthesise the glass-bound glycopolymer hydrogels, glyco-polymer hydrogels which consisted of 20% and 30% AGA, respectively, were combined with the remaining 100 mol% HEMA hydrogels as a control. Despite the glycopolymer's inside structure being exceedingly porous, the material's surface elacked evident porosity. To summarise, either a hydrogel, being the testing substrate or mucosal membrane, was inserted in a channel within a 37 degree C incubator. Then, fluorescein-labeled mucoadhesive polymers were pipetted onto the testing substrate. The testing substrate was then washed with an eluent of an appropriate simulated physiological fluid or PBS. 17,18. Chitosan and pectin were chosen as mucoadhesive polymers since they are regularly used as mucoadhesive agents. Additionally, these polymers were chosen because they are basic and acidic, indicating that they belong to two distinct families of mucoadhesive materials 19–21

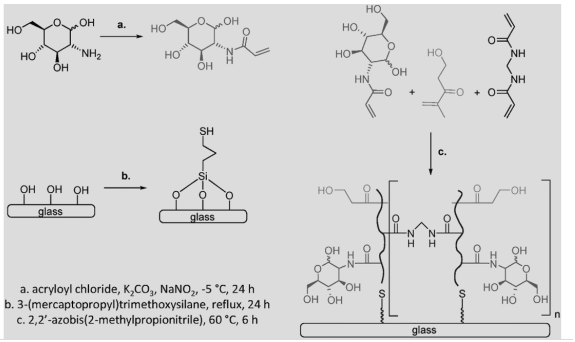

Figure 1: Synthetic route to glass-bound glycopolymer hydrogels.

4.2. Collagen gels

Collagen gel was placed on six-well plates, followed by three millimetre polycarbonate membrane inserts, followed by three millimetre collagen gel. After polymerization, gels were coated with Dulbecco's Modified Eagle Medium (DMEm) containing streptomycin, FCS, penicillin, ascorbic acid, human keratinocyte growth factor and incubated at 37 °C with 5% CO2 in a humidified atmosphere. After two days, NHOKs were inserted into each LPE. The mucous membrane models were lifted to the air-liquid interface after two days of immersion. A conventional growth medium was used to cultivate the plants. The cultivation of models was continued.29

4.3. Poly(acrylic acid) based hydrogels

Hydrogel coatings on glass slides are created by layer-by-layer (LbL) deposition of hydrogen-bonded interpolymer complexes formed by poly(acrylic acid) (PAA) and methylcellulose. Chemical modification with (3-aminopropyl)triethoxysilane on the glass surface allows for cross-linking of interpolymer complexes and LbL deposition. More deposition cycles and cross-linking conditions are necessary for a thicker coating. This is the point at which two-dimensional networks become three-dimensional networks.

Swelling degrees are greater with higher pH values, notably greater than 6.0. These coatings were used as models to investigate the adhesive properties of pharmaceutical tablets and, potentially, replicate the total adhesion effort required to remove mucoadhesives from porcine buccal mucosa.

Researchers are interested in a variety of applications for ultrathin hydrogel films, including the fabrication of functionalized and stimulus-responsive surfaces, gating devices, chemical sensors, actuators, drug delivery systems and cell encapsulation.
The LbL sequential deposition of water-soluble polymers on solid surfaces is one of the most effective methods for achieving ultra-thin coatings. To synthesise insoluble polyelectrolyte complexes, polyelectrolytes with oppositely charged charges were employed.

The most frequently used building blocks for LbL materials are polyacrylamide, PAA or poly(methacrylic acid) with polyethylene oxide, poly(N-vinyl pyrrolidone), poly(N-isopropyl acrylamide), poly(2-hydroxyethyl acrylate), poly(vinyl methyl ether) and poly(N-vinyl caprolactam). It was demonstrated that non-ionic cellulose ethers can also form hydrogen-bonded IPAs with PAA in acidic water. Hydroxyethylcellulose, methylcellulose, hydroxypropyl-cellulose and hydroxypropylmethylcellulose are all examples of non-ionic cellulose ethers.

Due to the non-stoichiometry of the complexes formed by cellulose ethers, an excessive amount of PAA is incorporated into the IPC structure. Complexation with cellulose ethers enables the use of IPCs in a variety of applications due to their industrial relevance, biocompatibility, and nontoxicity. Hydrogels were generated when PAA and methylcellulose (MC) were complexed. 63,64

LbL deposition was used to deposit polymeric complexes on a glass surface. When the polymeric complexes were heated, the polymers were cross-linked, resulting in ultrathin films that detached from the glass substrate when swelled. Monodisperse hollow microcapsules were created by LbL assembly of IPCs onto colloidal SiO2 particles and then removing the silica core with hydrofluoric acid. Planar glass substrates were constructed with covalently bonded hydrophilic polymeric layers via surface modification with (4-aminobutyl)dimethylmethoxysilane, absorption of

poly[(1-methylvinyl isocyanate)-alt-(maleic anhydride)] and subsequent reaction with poly(ethylene glycol) (PEG). Boric silicate glass is reacted with (3-aminopropyl)-triethoxy-silane and then coated with PEG-vinyl sulfone and dithiothreitol. 19,23,24 By layering PAA-MC complexes, ultrathin hydrogel coverings covalently attached to a glass surface can be generated.

4.4. GelMA Hydrogels

Co-cultured GelMA hydrogels containing human oral keratinocytes (HOKs) and human gingival fibroblasts (HGFs) were prepared for use in an artificial oral mucosal tissue model. A tissue engineering model of the oral mucosa was constructed using photocured GelMA and it was co-cultured with epithelial and fibroblast cells. To model the epithermal and dermal layers, HOKs and HGFs were employed. GelMA was cured using UV irradiation. This GelMA hydrogel may be utilised as a substitute for oral mucosal tissue.

Methacrylated gelatin was made after completely dissolving gelatin, followed by the addition of MA and letting the solution sit at room temperature for an additional hour. The reacted MA was extracted by dialysis with distilled water and lyophilized at 90 C for 7 days. Prior to in vitro cell cultivation, methacrylate gelatin was sterilised in 70% ethanol for 24 hours. The white powder was quantified using D2O and proton nuclear magnetic resonance (1 H NMR) analysis.

Normal HOKs were grown in T25 flasks with oral keratinocyte growth supplement and 1% penicillin/streptomycin in a 37 C incubator with 5% CO2. Cells were cultivated in the dark and the medium was replaced every other day with fresh medium. The fibroblast medium was supplemented with streptomycin (10mg/mL), 10% foetal bovine serum and penicillin. Every three days, a new medium was substituted. When the two cells achieved 70–80% confluence, they were removed from the culture flasks using 0.1% Ethylenediaminetetraacetic acid (EDTA) and 0.5% trypsin solutions. After two washes, the cells were employed for in vitro cell studies.

The three-dimensional reconstruction of an artificial oral mucosal tissue model was performed using a photocured GelMA hydrogel containing HGF. 300mL of each GelMA solution was separated and put into Millicell plates with a diameter of 12 mm. Hydrogel-loaded Transwell inserts were grown in a 6-well plate with HGF growth media. Every other day, fresh media was replenished on an inverted fluorescence microscope for 1, 3 and 5 days. Millicell plates were seeded with cell-laden hydrogels. The dermal-epidermal equivalent was created in this manner. 53,66

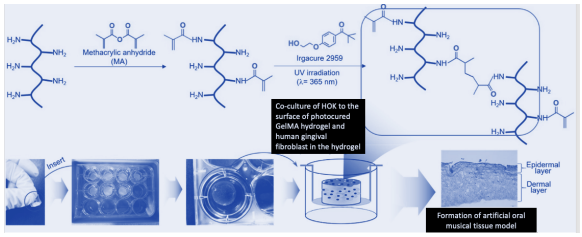

Figure 2: Preparation of methacrylated gelatin (GelMA) hydrogel by co-culture of human oral keratinocytes (HOKs) and human gingival fibroblasts (HGFs) for an oral mucosal tissue model.

.4.5. Polymeric and Cellulosic buccal membranes

- The solubility of carvedilol was evaluated using octanol, propylene glycol, and McIlvaine's buffer.47
- A little increase in pH and propylene glycol mixing (propylene glycol: 1:3:7) had the largest influence on carvedilol's solubility.
- After 24 hours of centrifugation at 1000 rpm, the supernatant was filtered using a 0.45 m membrane filter.
- The quantity of carvedilol in the samples was determined using UV spectrophotometry. 49
- The effect of the enhancer at three concentrations (0.1, 0.3, and 0.5 mg/mL) on the solubility of sodium taurodeoxycholate (STDC), sodium taurocholate (STC), camphor and menthol was investigated. Menthol and camphor were dissolved in a 20:80 mixture of ethanol and McIlvaine's buffer, commonly referred to as the McIlvaine buffer.50,51
- To determine carvedilol's solubility, a water solution was produced in which propylene glycol, octanol and McIlvaine buffer solutions were all evaluated at various pH levels.
- McIlvaine's pH 6.5 buffer (20:80, 40:60, 60:40, and 80:20) was centrifuged and filtered through a 0.45 m membrane filter after 24 hours of shaking in a thermostatic water bath shaker at 37 1 °C in the dark.

The study examined medication solubility using three different concentrations of an enhancer: 0.1, 0.3, and 0.5 mg/mL.52

5. Observation and Analysis

5.1. Glycopolymer hydrogels

Utilising two-way analysis of variance along with Bonferroni post hoc testing, it was indicated that a hydrogel containing 20% glass and swine stomach tissue did not exhibit statistically significant differences from animal mucosa. The retention of FITC-dextran , a non-mucoadhesive control on stomach mucosa was not statistically different between gastric fluid, phosphate buffer solution (PBS) and simulated gastric juice (SGJ). FITC-dextran controls had no relationship with the glass-bound hydrogels and their connection with the bovine cornea. When tested in artificial tear fluid containing chitosan, it looked much like a bovine cornea. In this solution, the solubility of chitosan is poor, which helps the retention of chitosan on PTFE. In all non-control substrates and eluent systems, pectin appears to be preserved more effectively 22–24

It is believed that, even though there is no dependence on rheological and solubility effects, the main reason why 20 mol percent AGA hydrogels are effective for pig stomach mucosa is due to interactions between the hydrogel and its components, which are brought about by the presence of a glycomonomer within the hydrogel. Hydrogen bonding and hydrophobic interactions are the primary forces that govern these interactions, along with ion dipole and electrostatics. The hydrogel may include glycomonomer pendant groups that resemble oligosaccharides. AGA tetrasaccharides have a similar constitution to these tetrasaccharides. While additional support for mucoadhesion is provided by physical entanglement, the network structure has an influence on retention as well. While 30% AGAG performed poor mimics of the mucosae, the increase in AGAG concentration allowed for more intense swelling, resulting in reduced polymer volume fraction, and led to a weakening of the network structure. The mucoadhesive polymers have better adherence and retention on porcine gastric mucosa compared to bovine cornea. A simulated cornea mimic would have been impossible to make because of the lack of a secretory mucus layer. A swine stomach mucosa-mimicking substance has been developed for mucoadhesion studies. This is based on a glass-bound hydrogel containing 80% HEMA and 20% AGA. 25

5.2. Collagen gels

An in vitro three-dimensional non keratinized mucous membrane model was created that closely resembles the natural oral mucosa of humans. This model system consists of an oral mucosa with many epithelial layers, a basement membrane, and a stratified squamous epithelium.30

The model was grown without the addition of calcium pantothenate or dexpanthenol to culture conditions to induce proliferation. The absence of calcium pantothenate and dexpanthenol had no effect on the creation of 3D mucous membrane models. Without the use of calcium pantothenate or dexpanthenol, mucous membrane models can be cultured for up to 5 days. On performing immune fluorescence, the oral mucosa model coloured similarly to natural mucosa, demonstrating its ability to mimic in vivo tissue. After four days of coculture, laminin 5, collagen IV, and 4-integrin exhibited linear deposition. CK5 staining occurs exclusively in the basal to suprabasal levels of the stratum spinosum, whereas CK13 staining occurs in all cell layers except the basal cell layer. Ki67 is a marker of basal cell proliferation. As previously noted, no differences in staining patterns were seen when the model was grown in medium without dexpanthenol and calcium pantothenate.31–33

5.3. Poly(acrylic acid) based hydrogels

When just detachment pressures are addressed, very simple plastic materials like polypropylene plates can occasionally exhibit mucosa-mimetic features. Although the ultra-thin hydrogel coverings created in this work demonstrated some ability to replicate the entire work of adhesion, their detachment profiles did not like those of porcine mucosa. It is believed that the detachment profiles for a particular dosage form can be regarded as iconic for mucosal adhesion, as they provide a comprehensive description of the

mucoadhesive performance. The findings suggest that more improvements in mucosa-mimetic properties may be possible by employing thicker hydrogel samples with porosity, optimised swelling properties, elasticity and hydration levels.

5.4. GelMA Hydrogels

By selectively attaching to integrins involved in cell adhesion, gelatin, one of the key sugar proteins, regulates cellular responses such as cell survival, differentiation, growth and death. Increasing cell adhesion, motility, proliferation, and differentiation may aid in the optimization of tissue regeneration. GelMA hydrogel is advantageous for three-dimensional cell culture due to its structure, which allows for adequate room for cell adhesion and growth.

The co-cultured HGF and HOK GelMA hydrogel generated a bi-layered oral mucosal tissue in this study. To aid co-cultured keratinocytes in adhesion, fibroblasts in gelatin sponge create laminin and fibronectin. Furthermore, fibroblasts have the ability to release cytokines such as keratinocyte growth factors and beta-transforming growth factors. However, the GelMA hydrogel co-cultured with HOK and HGF must be an advanced oral mucosal tissue model in vitro. The growth of in vitro alternatives to animal skin models has increased in recent years. The current study's cell-cultured hydrogel method may be used in place of oral mucosal animal models. This work has been validated in vivo animal models. 58,59

5.5. Polymeric and Cellulosic buccal membranes

Carvedilol is marginally to sparingly soluble in octanol and essentially insoluble in water and McIlvaine's buffer, as determined by us (pH 6.5) These findings corroborated prior studies. Propylene glycol was utilised as a cosolvent to obtain solubility close to the maximal aqueous-buffer solubility (1.91 mg/mL) for the buccal mucosa. In general, solubilization with bile salts was greater than that with terpenes at higher enhancer doses (0.3 and 0.5 mg/L) (P 0.05). Our CMC tests indicate that the high solubility of STDC and STC is due to their surfactant properties and the trapping of carvedilOL. 54,64,65

The permeation through the cellulose acetate membrane was significantly greater than the permeation through the cellulose nitrate membrane (t-test; P 0.05). The acetate-nitrate combination membrane demonstrated greater steady-state flow values and a shorter lag time than the cellulose acetate membrane. Due to its larger pore size and greater degree of porosity (pore size of 0.2m, thickness 110m, and permeability of 90% vs. cellulose acetate-nitrate mixture membrane pore size of 0.025m, thickness 70m, and permeability of 70%), it was projected to have a higher permeability and a shorter lag time. The permeability of carvedilol to lipophilic compounds (table II) was comparable to that of swine buccal mucosa (table I).41,53

The combination of cellulose acetate and nitrate has an inherent permeability value of 59.8 (*10-5 cm min-1) and 60.12, respectively. Artificial membranes can be used to investigate permeability and serve as models for buccal mucosa penetration. When conducting permeability tests, it is critical to consider the kind of membrane, the treatment conditions, and the experimental design. When the paracellular route is disrupted, the lag time required to initiate penetration through artificial membranes increase.41,44

Pretreatment of artificial membranes with phosphatidylethanolamine in octanol to mimic the lipophilicity of natural membranes increased lag times significantly. The addition of permeation enhancers (STDC, STC, menthol, or camphor) led to an increase in permeability in a similar order to that reported with natural mucosa. For bile salts and terpenes, the permeability enhancement effect can be explained by the creation of micellar systems and eutectic mixtures, respectively. We found a linear connection between the permeability coefficients of natural mucosas and lipid-imparted artificial membranes in the presence and absence of enhancers. Between natural mucosal and artificial membranes, the same linearity was found for steady-state flow and permeability enhancement ratio. 54,55

6. Conclusion

The conjecture is that it is due to the lack of structural and mechanical resemblance, which suggests that the

capacity to resemble mucosal tissue is due to the presence of specific groups with particular oligosaccharide content, which is seen in secretory mucous glycoproteins that have a high glycosylation level 26Using this chemical could help researchers to assess the efficacy of mucoadhesive dose formulations prior to clinical trials, leading to a significant reduction in the number of animals engaged in mucoadhesion studies 5,27,28

Keratinized hard palate cells were grown into a full-thickness oral mucosa model. Using cells from the inside of the cheeks, they created a non keratinized mucous membrane model. Numerous previous models did not completely replicate normal oral mucosa and required dexpanthenol or calcium pantothenate to stimulate proliferation in the culture media. The model has the advantage of not requiring calcium pantothenate or dexpanthenol for cultivation. Additionally, this mucous membrane model was developed as a standard for evaluating the therapeutic and biological effects of wound care products, which almost exclusively contain dexpanthenol. Pantothenic acid and Dexpanthenol are frequently used in clinical practise because they have been shown to improve wound healing by enhancing the proliferation of dermal fibroblasts and epidermal keratinocytes. Dexpanthenol is a humectant that aids in the reduction of transepidermal water loss. Dexpanthenol has been shown to mitigate the ciliary and cytotoxic effects of -sympathomimetic decongestants.34,35

The three-dimensional mucous membrane models were treated with a placebo ointment or 5% dexpanthenol ointment without dexpanthenol and were compared to an untreated model. Models treated with the dexpanthenol-containing ointment displayed significantly improved wound healing compared to models treated with a placebo emulsion without dexpanthenol or the ointment-untreated control. Dexpanthenol has also been demonstrated to induce skin regeneration and improve wound healing

Microarray analysis was employed to corroborate our findings. The findings indicated that laser injury and therapy with a dexpanthenol-containing ointment enhanced the expression level of the main chemokine CXCL-10. Chemokines influence neutrophil migration to wounds during acute inflammatory responses. Additionally, it has been demonstrated that chemokines influence epithelialization, tissue remodelling and angiogenesis, making them important modulators of wound healing. Mucins are glycosylated proteins found in the mucus layer surrounding epithelial cells in a variety of human and animal tissues, including the oral cavity. They observed an increase in the expression of mucin family members in our animals when dexpanthenol-containing ointment was used. The results indicate that the dexpanthenol-containing ointment contributes to the formation of the mucus layer, an increase in retinoic acid receptor responder 1 expression (RARRES1). The retinoic acid metabolite of vitamin A has been shown to enhance wound healing processes including inflammation, proliferation and differentiation. Retinoic acid modulates transcription via interacting with the retinoic acid receptor and its isoforms. In the skin, a newly found retinoic acid receptor-regulated gene exhibits tumour suppressive activity.

Finally, it was concluded that, on comparing it to untreated and placebo ointment-treated controls, ointment containing 5% dexpanthenol promotes wound closure in our newly developed mucous membrane model. On examining the molecular effects of a 5% dexpanthenol-containing ointment, changes in wound healing-related gene expression on our mucous membrane model was discovered.

Lesions scanned with a CO2 laser can be used to assess wound healing outcomes. To ascertain the effect of topically applied B5 on gene expression, morphology , skin wound healing, ex vivo experiments could be utilised to investigate B5 effects on skin wound healing, gene expression and morphology.

Although a perfect mucosa-mimetic material was not achieved, thus provided useful information about the further development of mucosa-mimicking materials and understanding the adhesion phenonema.20

Hydrogels are well-known synthetic skin models used to cultivate dermal fibroblasts. Hydrogels are used to promote the growth of skin cells on the surface. Hydrogel models have demonstrated biomimetic functionalities and are more cost effective

than microfluidic devices. As a result, hydrogels make excellent scaffolding for oral mucosal tissue.

A photocured GelMA hydrogel co-cultured with HGF and HOK was produced and its efficacy was evaluated as a tissue model in vitro. Due to the biocompatibility of the GelMA hydrogel, HGF and HOK cells attached to and proliferated on both the hydrogel's bulk and surface. It is believed that co-culturing GelMA hydrogel with HOK and HGF is a suitable model for oral mucosal tissue.37–40

Artificial polymeric membranes may be used to predict drug penetration via buccal mucosa and the influence of permeation enhancers on the penetration process. The employment of synthetic saliva in the donor compartment and synthetic plasma in the receiver compartment may be deemed more realistic. There was no linear link between membranes and the effect of permeation enhancers on the drug penetration process across diverse experimental groups.47,56,57

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